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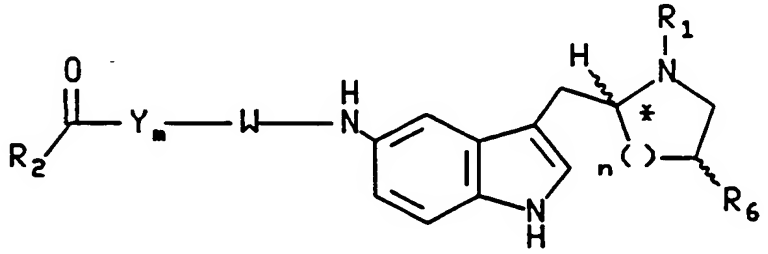

(I)

(57) Abstract

Compounds of formula (I) where n is 0, 1, or 2; m is 0 or 1; Y and W are each an amino acid residue; R_1 is hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, aryl, C_1-C_3 alkylaryl, or C_1-C_3 alkylheteroaryl, and -$(CH_2)_pR_3$; R_2 is CF_3, C_1-C_6 alkyl, aryl, C_1-C_3 alkylaryl, and -OR_5; R_3 is cyano, trifluoromethyl, or -OR_4; R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_5 is C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_6 is hydrogen, -OR_7, or -$NHCOR_7$; R_7 is hydrogen, C_1 to C_6 alkyl, aryl, or C_1 to C_3 alkyl-aryl; p is 1, 2, or 3; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamide, nitro, and C_1 to C_4 alkoxy and the pharmaceutically acceptable salts thereof. These compounds are useful in treating migraine and other disorders. These compounds are useful psychotherapeutics and are potent serotonin (5-HT_1) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators.

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ACYLAMINOINDOLE DERIVATIVES AS 5-HT1 AGONISTS

Background of the Invention

The present invention relates to indole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating migraine and other disorders.

United States Patents 4,839,377 and 4,855,314 and European Patent Application Publication No. 313397 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent Application 040279 refers to 3-aminoalkyl-1H-indole-5-thioamides and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Application Publication No. 303506 refers to 3-poly:hydro-pyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT_1 receptor agonist and vasoconstrictor activity and to be useful in treating migraine.

European Patent Application Publication No. 354777 refers to N-piperidinyl:indolyl:ethyl-alkane sulfonamide derivatives. The compounds are said to have 5-HT_1 receptor agonist and vasoconstrictor activity and to be useful in treating cephalic pain.

European Patent Applications Publication Numbers 438230, 494774, and 497512 refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have 5-HT_1-like receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

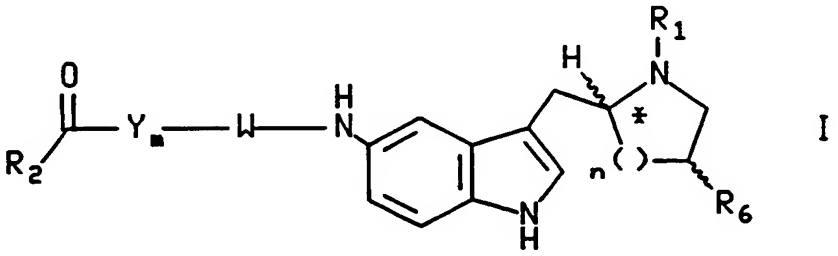
International Patent Application PCT/GB91/00908 and European Patent Application No. 313397A refers to 5-heterocyclic indole derivatives. The compounds are said to exhibit properties useful in the treatment and prophylaxis

of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have "5-HT_1-like" receptor agonism.

European Patent Application Publication No. 457701 refers to certain aryloxyamine derivatives as having a high affinity for 5-HT_{1D} serotonin receptors. These compounds are said to be useful in treating diseases related to 5-HT receptor disfunction, especially migraine.

Summary of the Invention

The present invention relates to compounds of the formula



I

where n is 0, 1, or 2; m is 0 or 1; Y and W are each an amino acid residue (including naturally occurring amino acids such as alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparginine, glutamine, aspartic acid, glutamic acid, lysine, arginine, or histidine); R_1 is hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, aryl, C_1-C_3 alkylaryl, or C_1-C_3 alkylheteroaryl, and -$(CH_2)_pR_3$; R_2 is CF_3, C_1-C_6 alkyl, aryl, C_1-C_3 alkylaryl, and -OR_5; R_3 is cyano, trifluoromethyl, or -OR_4; R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_5 is C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R^6 is hydrogen, -OR_7, or -$NHCOR_7$; R_7 is hydrogen, C_1 to C_6 alkyl, aryl, or C_1 to C_3 alkyl-aryl; p is 1, 2, or 3; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen (e.g. fluorine, chlorine bromine

or iodine), hydroxy, cyano, carboxamide, nitro, and C_1 to C_4 alkoxy and the pharmaceutically acceptable salts thereof. These compounds are useful in treating migraine and other disorders.

The compounds of the invention include all optical isomers of formula I (e.g., R and S stereogenicity at any chiral site) and their racemic, diastereomeric, or epimeric mixtures. When R_6 is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula I are preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is O or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula I are preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula I are preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is O, the <u>cis</u> epimers [(2S, 3S) absolute configuration in the azetidine ring] are particularly preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 1, the <u>cis</u> epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 2, the <u>cis</u> epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly preferred.

Unless otherwise indicated, the alkyl, alkenyl, and alkynyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g. alkoxy), may be linear or branched, and they may also be cyclic (e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) or be linear or branched and contain cyclic moieties.

Preferred compounds of the invention are compounds of the formula I wherein n is 1; m is 0; the amino acid is a naturally occurring amino acid; R_1 is hydrogen, C_1-C_4 alkyl, or $-CH_2CH_2OCH_3$; R_2 is C_1-C_4 alkyl, -Ph (Ph=phenyl), $-CF_3$, or $-OR_5$. Of the foregoing preferred compounds, when R_6 is hydrogen, the epimers with the R absolute configuration at

the chiral carbon site designated by an asterisk in formula I are more preferred. Of the foregoing preferred compounds, when R_6 is $-OR_7$ or $-NHCOR_7$, the epimers with the S absolute configuartion at the chiral carbon site designated by an asterisk in formula I are more preferred. Of the foregoing compounds, when R_6 is $-OR_7$ or $-NHCOR_7$, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred.

The following compounds are particularly preferred:

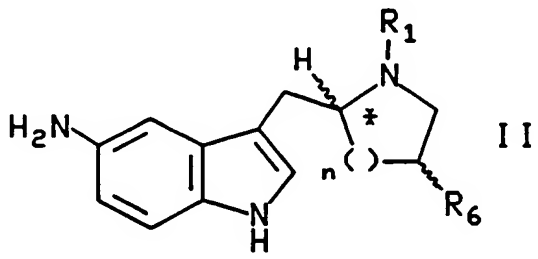
5-(N-benzyloxycarbonylglycyl)amino-3-(N-methylpyrrolidin-2-(R)-ylmethyl)-1H-indole;

5-(N-benzyloxycarbonyl-(S)-histidyl)amino-3-(N-methylpyrrolidin-2-(R)-ylmethyl)-1H-indole;

5-(N-benzyloxylcarbonyl-(S)-phenylalanyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole; and

5-(N-benzyloxycarbonyl-(S)-alanyl)amino-3-(N-methylpyrrolidin-2-(R)-ylmethyl)-1H-indole.

The present invention also relates to a compound of the formula



II

where n is 0, 1, or 2; R_1 is hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, aryl, C_1-C_3 alkylaryl, or C_1-C_3 alkylheteroaryl, and $-(CH_2)_pR_3$; R_3 is cyano, trifluoromethyl, or $-OR_4$; R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_6 is hydrogen, $-OR_7$, or $-NHCOR_7$; R_7 is hydrogen, C_1 to C_6 alkyl, aryl, or C_1 to C_3 alkyl-aryl; p is 1, 2, or 3; a chiral carbon is designated by as asterisk; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be

substituted with one to three groups selected from C_1 to C_4 alkyl, halogen (e.g. fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamide, nitro, and C_1 to C_4 alkoxy. When R_6 is hydrogen, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula II are preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 0 or 1, the epimers with the S absolute configuration at the chiral carbon site designated by an asterisk in formula II are preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 2, the epimers with the R absolute configuration at the chiral carbon site designated by an asterisk in formula II are preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 0, the cis epimers [(2S, 3S) absolute configuration in the azetidine ring] are particularly preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 1, the cis epimers [(2S, 4R) absolute configuration in the pyrrolidine ring] are particularly preferred. When R_6 is $-OR_7$ or $-NHCOR_7$ and n is 2, the cis epimers [(2R, 5R) absolute configuration in the piperidine ring] are particularly preferred. These compounds are useful as intermediates in preparing compounds of formula I.

The present invention also relates to a pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition and a pharmaceutically acceptable carrier.

The present invention also relates to a method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal (e.g., a human) requiring such

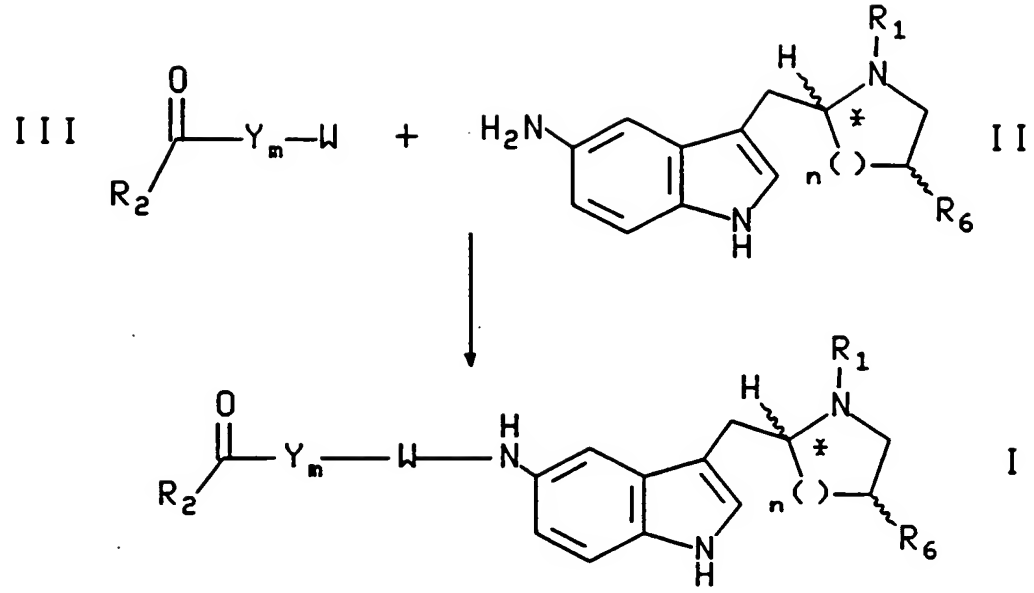
treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

The present invention also relates to a pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

The present invention also relates to a method for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

Detailed Description of the Invention

The compounds of the present invention can be prepared as shown in the following reaction scheme:

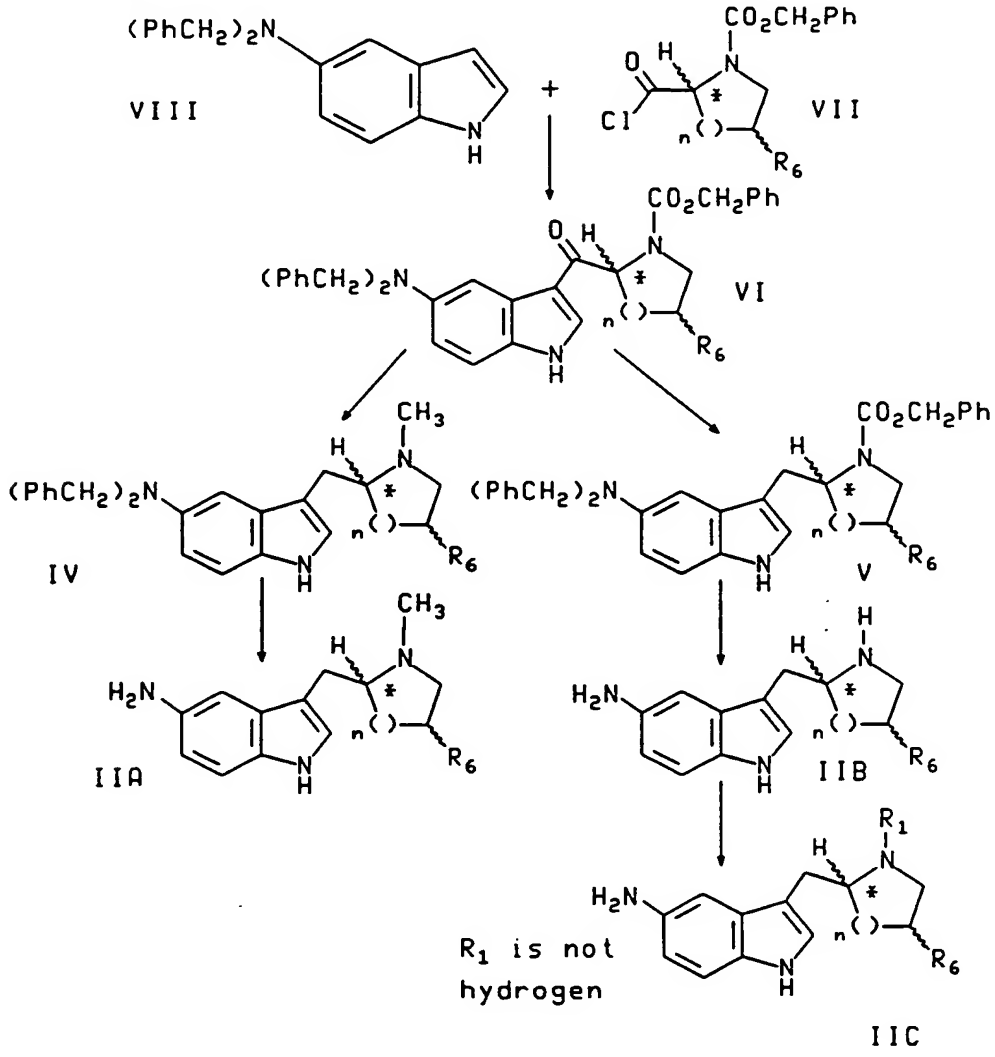


Compounds of formula I are prepared by the coupling reaction of a compound of formula II where n, R_1, and R_6 are as defined above with a compound of the formula III where m, R_2, Y, and W are as defined above with Y and W having a C terminal on the right side and an N terminal on the left side of each residue, the C terminal of W being in the carboxylic acid form. The reaction is carried out in the presence of a carboxylic acid activating agent in an inert solvent. Suitable carboxylic acid activating agents include oxalyl chloride, thionyl chloride, carbonyldiimidazole, dicyclohexylcarbodiimide, and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide. The preferred carboxylic acid activating agent is carbonyldiimidazole. Suitable solvents include diethyl ethyl, tetrahydrofuran, 1,4-dioxane, chloroform, methylene chloride, or N,N-dimethylformamide. The preferred solvent is methylene chloride. The reaction is run at a temperature of from about 0°C to about 65°C, preferably at about 25°C (room temperature).

Compounds of the formula III are either commercially available or can be prepared using methods known in the art,

for example, as described in M. Bodanszky, Peptide Synthesis, John Wiley and Sons, New York (1976).

Compounds of formula II can be prepared as shown in the following reaction scheme:



Compounds of formula IIC where n and R_6 are as defined above and R_1 is as defined above but for hydrogen are prepared by the alkylation of a compound of formula IIB where n and R_6 are as defined above with an alkylating agent and a base in an inert solvent. Suitable alkylating agents include alkyl halides (chlorides, bromides, or iodides), alkyl tosylates, alkyl mesylates, alkyl triflates, α,ß-unsaturated ketones, α,ß-unsaturated esters, α,ß-unsaturated

aldehydes, α,β-unsaturated amides, and α,β-unsaturated nitriles. Alkyl halides (iodides) are preferred. Suitable solvents include methylene chloride, chloroform, carbon tetrachloride, acetonitrile, tetrahydrofuran, diethyl ether, dioxane, N,N-dimethylformamide, ethanol, propanol, methanol. The preferred solvent is acetonitrile. The reaction is conducted between a temperature of about 0°C to about 150°C preferably about 0°C to about 25°C.

Compounds of formula IIA where n and R_6 are as defined above are prepared by catalytic reduction of a compound of formula IV where n and R_6 are as defined above under an atmosphere of hydrogen, preferably at a pressure of about 1 to about 3 atmospheres, or using a hydrogen source such as ammonium formate or formic acid in an inert solvent. Suitable catalysts include palladium on carbon, palladium hydroxide on carbon, Raney nickel, and platinum oxide. The preferred catalyst is palladium hydroxide on carbon. Suitable solvents include C_1 to C_6 alcohols, N,N-dimethylformamide, ethyl acetate, and acetonitrile. The preferred solvent is ethanol. The reaction is conducted at a temperature of about 0°C to about 100°C, most preferably at about 50°C.

Compounds of formula IIB where n and R_6 are as defined above are prepared by catalytic reduction of a compound of the formula V where n and R_6 are as defined above under an atmosphere of hydrogen, preferably at a pressure of about 1 to about 3 atmospheres, or using a hydrogen source such as ammonium formate or formic acid in an inert solvent. Suitable catalysts include palladium on carbon, palladium hydroxide on carbon, Raney nickel, and platinum oxide. The preferred catalyst is palladium hydroxide on carbon. Suitable solvents include C_1 to C_6 alcohols, N,N-dimethylformamide, ethyl acetate, and acetonitrile. The preferred solvent is ethanol. The reaction is conducted at a temperature of about 0°C to about 100°C, most preferably at about 50°C.

Compounds of formula IV are prepared via the hydride reduction of a compound of the formula VI using methods known in the art, for example, as described in W. A. Reimers, "Indole Aldehydes and Ketones" in the series The Chemistry of Heterocyclic Compounds, Volume 25, Part III, Weissberger, A. and Taylor, E. C. (eds), John Wiley and Sons, New York, pp. 403-405 (1979).

Compounds of formula V are prepared via the hydride reduction of a compound of the formula VI using methods known in the art, for example, as described in W. A. Reimers, "Indole Aldehydes and Ketones" in the series The Chemistry of Heterocyclic Compounds, Volume 25, Part III, Weissberger, A. and Taylor, E. C. (eds), John Wiley and Sons, New York, pp. 403-405 (1979).

Compounds of formula VI are prepared using methods known in the art, for example, as described in W. A. Reimers, "Indole Aldehydes and Ketones" in the series The Chemistry of Heterocyclic Compounds, Volume 25, Part III, Weissberger, A. and Taylor, E. C. (eds), John Wiley and Sons, New York, pp. 388-389 (1979).

Compounds of the formula VII are using prepared methods known in the art, for example, as described in Aoyama, T. and Shioiri, T., Chem. Pharm. Bull, 3249 (1981). Other halogens can be used in place of chloride in formula VII and are prepared using methods known in the art, however, chloride is preferred.

Compounds of formula VIII are prepared using methods known in the art, such as, for example, as disclosed in Example 8.

The $-CO_2CH_2Ph$ group in compound of formula VII and the $PhCH_2-$ groups in compound of formula VIII are protecting groups for the nitrogen atoms in each of the respective compounds and are preferred. Other protecting groups include $-COCF_3$, $-COCH_2CCl_3$, $-CO_2C(CH_3)_3$ and $-CH_2OCH_2Ph$. Compounds of formulae VII and VIII having these other protecting groups can be prepared using methods known in the

art. Removal of these other protecting groups to form compounds of formulae IIA, IIB and IV can also be accomplished using methods known in the art, for example, as described in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley and Sons, New York (1981), pp. 218-287.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, i.e., where W contains a carboxylate, are capable

of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particular, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium, magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction of maximum product of yields of the desired final product.

The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to as the active compounds of the invention) are useful psychotherapeutics and are potent serotonin (5-HT_1) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, chronic paroxysmal hemicrania and headache associated with vascular disorders, pain, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators. The active compounds of the invention can be evaluated as anti-migraine agents by testing the extent to which they mimic

sumatriptan in contracting the dog isolated saphenous vein strip [P.P.A. Humphrey et al., Br. J. Pharmacol., 94, 1128 (1988)]. This effect can be blocked by methiothepin, a known serotonin antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anesthetized dog. It has been suggested [W. Fenwick et al., Br. J. Pharmacol., 96, 83 (1989)] that this is the basis of its efficacy.

The serotonin 5-HT_1 agonist activity is measured in in vitro receptor binding assays as described for the 5-HT_{1A} receptor using rat cortex as the receptor source and [^{3}H]-8-OH-DPAT as the radioligand [D. Hoyer et al. Eur. J. Pharm., Vol. 118, 13 (1985)] and as described for the 5-HT_{1D} receptor using bovine caudate as the receptor source and [^{3}H]serotonin as the radioligand [R.E. Heuring and S.J. Peroutka, J. Neuroscience, Vol. 7, 894 (1987)]. 5-HT_1 agonist activity is defined by agents with affinities (IC_{50}) of 250 nM or less with either binding assay.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, sublingual, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch

glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal and sublingual administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or

pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., migraine) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult are preferably arranged so that each metered dose or "puff" of aerosol contains 20μg to 1000μg of the compound of the invention. The overall daily does with an aerosol will be within the range 100 μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The following Examples illustrate the preparation of the compounds of the present invention. Commercial reagents were utilized without further purification. Chromatography refers to column chromatography preformed using 32-63μm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room temperature refers to 20-25°C.

EXAMPLE 1

General Procedure for the Coupling of Amino Acid Derivatives with 5-Aminoindole Derivatives

To a stirred mixture of the N-protected amino acid (1.1 mmol, 1.4 eq) in anhydrous methylene chloride (5 mL) was added carbonyl diimidazole (180 mg, 1.4 mmol, 1.1 eq). The reaction mixture was stirred at room temperature under nitrogen until the reaction solution became clear (15 minutes to 24 hours, depending on the substrate), at which time the appropriate 5-aminoindole derivative (0.80 mmol) was directly added to the reaction solution. The resulting reaction solution was stirred at room temperature under nitrogen for 2 hours, and then it was directly chromatographed using silica gel (approximately 20 g) and elution with CH_2Cl_2/CH_3OH/triethylamine [8:1:1] to afford the coupled amino acid/5-amino indole derivative.

Using this procedure, the following compounds were prepared.

A. 5-(N-Benzyloxycarbonylglycyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

N-Benzyloxycarbonylglycine and 5-amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole were used. Chromatography as described above afforded the title compound as a clear, pale red foam (74%): R_f=0.3 in CH_2Cl_2/CH_3OH/triethylamine [8:1:1]; ^1H NMR ($CDCl_3$) δ 9.25 (br s, NH), 9.08 (br s, NH), 7.69 (s, 1H), 7.28 (br s, 5H), 7.12 (d, J=8.8Hz, 1H), 7.08 (d, J=9.3Hz, 1H), 6.88 (br s, 1H), 6.32 (br t, NH), 5.09 (s, 2H), 3.99 (br d, J=4.8Hz, 2H), 3.07-3.00 (m, 2H), 2.56-2.36 (m, 2H), 2.36 (s, 3H), 2.16 (dd, J=8.7 and 17.3 Hz, 1H), 1.76-1.44 (m, 4H); LRMS (m/z, relative intensity) 420 (2), 418 (22), 310 (4), 228 (4), 171 (13), 108 (25), 84 (100); HRMS calculated for $C_{24}H_{28}N_4O_3$ 420.216, found 420.208.

B. 5-(N-benzyloxylcarbonyl-S-histidyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

N-Benzyloxycarbonyl-S-histidine and 5-amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole were used.

Chromatography as described above afforded the title compound (46%) as an pale yellow foam: R_f=0.4 in CH_2Cl_2/CH_3OH/ammonium hydroxide [8: 2: 0.1]; ^{13}C NMR (CD_3OD) δ 172.3, 158.3, 138.1, 136.2, 135.7, 130.7, 129.5, 129.0, 128.8, 128.6, 124.8, 117.3, 113.4, 112.3, 68.4, 67.7, 58.3, 57.3, 40.9, 32.2, 31.2, 30.2, 22.4; FAB LRMS (m/z, relative intensity) 501 ([MH^+], 100), 417 (4), 367 (6), 309 (4), 273 (6). Anal. calcd for $C_{28}H_{32}N_6O_3 \cdot 0.25\ H_2O$; C, 66.58; H, 6.49; N, 16.63. Found: 66.47; H, 6.56; N, 16.48.

C. 5-(N-benzyloxylcarbonyl-S-alanyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

N-Benzyloxycarbonyl-S-alanine and 5-amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole were used. Chromatography as described above afforded the title compound (33%) as a white foam: R_f=0.1 in CH_2Cl_2/CH_3OH/ammonium hydroxide [9: 1: 0.1]; ^{13}C NMR ($CDCl_3$) δ 177.9, 155.9, 138.6, 136.8, 131.4, 128.4, 127.9, 127.6, 124.0, 113.3, 112.3, 109.1, 103.5, 68.6, 66.4, 56.1, 51.3, 39.7, 30.4, 26.4, 21.4, 19.4. Anal. calcd for $C_{25}H_{30}N_4O_3 \cdot 0.5$ ethyl acetate [$C_4H_8O_2$]$\cdot 0.5$ methylene chloride [CH_2Cl_2]: C, 63.42; H, 6.77; N, 10.75. Found: C, 63.45; H, 6.72; N, 10.79.

D. 5-(N-benzyloxylcarbonyl-S-phenylalanyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole

N-Benzyloxycarbonyl-S-phenylalanine and 5-amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole were used. Chromatography as described above afforded the title compound (90%) as a white foam: R_f=0.7 in CH_2Cl_2/CH_3OH/ammonium hydroxide [9: 1: 0.1); ^{13}C NMR ($CDCl_3$) δ 169.4, 156.2, 136.6, 136.1, 134.0, 129.4, 129.0, 128.7, 128.5, 128.2, 128.0, 127.6, 127.0, 123.4, 116.5, 113.6, 111.4, 111.3, 67.1, 66.6, 57.4, 57.1, 40.7, 39.1, 31.4, 29.6, 21.8; FAB LRMS (m/z, relative intensity) 511 ([MH^+], 77), 281 (11), 147 (100); HRMS calculated for [$C_{31}H_{34}N_4O_3 \cdot H$]$^+$ 511.2712, found 511.2687. Anal. calcd for $C_{31}H_{34}N_4O_3 \cdot 0.75\ H_2O$: C, 71.04; H, 6.83; N, 10.69. Found: C, 71.20; H, 6.88; N, 10.72.

EXAMPLE 2

General Procedure for the Alkylation of 5-Amino-(R)-3-(pyrrolidin-2-ylmethyl)-1H-indole Forming 5-Amino-(R)-3-(N-alkylpyrrolidin-2-ylmethyl)-1H-indoles

To a stirred solution of 5-amino-(R)-3-(pyrrolidin-2-ylmethyl)-1H-indole (1.00 mmol) and triethylamine (0.126 g, 1.25 mmol, 1.25 eq) in either anhydrous methylene chloride, anhydrous acetonitrile, absolute ethanol, or i-propanol (10 mL) at room temperature under nitrogen is added dropwise the alkylating agent (1.25 mmol). The resulting reaction solution is then stirred under nitrogen at room temperature for 1 to 20 hours, depending on substrate. The resulting reaction mixture is directly column chromatographed using silica gel (approximately 25 g) and elution with methylene chloride; methanol: ammonium hydroxide [9:1:0.1] to afford the 5-amino-(R)-3-(N-alkylpyrrolidin-2-ylmethyl)-1H-indole.

EXAMPLE 3

(R)-5-Amino-3-(pyrrolidin-2-ylmethyl)-1H-indole

A mixture of (R)-3-(N-benzyloxycarbonylpyrrolidin-2-ylmethyl)-5-dibenzylamino-1H-indole (7.90 g, 14.91 mmol) and moist palladium (II) hydroxide on carbon (Pearlman's catalyst, 3.16 g) in absolute ethanol (100 mL) was shaken under a hydrogen atmosphere (3 atm) for 12 hours at room temperature. The resulting mixture was filtered through diatomaceous earth, and the filtrate was evaporated and dried under reduced pressure to afford the title compound as a white foam (3.20 g, 100%): ^{1}H NMR (CD_3OD) δ 7.18 (d, J=8.5 Hz, 1H), 7.08 (s, 1H), 6.92 (d, J=2.0 Hz, 1H), 6.69 (dd, J=1.9 and 8.5 Hz, 1H), 3.81-3.69 (m, 1H), 3.30-2.95 (m, 4H), 2.09-1.55 (m, 4H); ^{13}C NMR (CD_3OD) δ 140.1, 133.4, 129.1, 125.0, 114.6, 113.1, 109.8, 105.1, 62.1, 46.0, 31.1, 29.1, 24.3; LRMS (m/z, relative intensity) 215 (M^+, 2), 198 (1), 146 (100), 128 (7), 117 (9), 70 (60).

EXAMPLE 4

(R)-3-(N-Benzyloxycarbonylpyrrolidin-2-ylmethyl)-5-dibenzylamino-1H-indole

To a stirred solution of (R)-3-(N-benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-dibenzylamino-1H-indole (1.50 g, 2.75 mmol) in anhydrous tetrahydrofuran (30 mL) was added lithium borohydride (0.24 g, 11.0 mmol, 4.0 eq) as a solid. The resulting reaction mixture was heated at reflux for 4 hours. A saturated solution of sodium hydrogen carbonate (10 mL) was then added, and this mixture was stirred at room temperature for 30 minutes. This aqueous mixture was then extracted with ethyl acetate (3 x 25 mL), and the organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residue using silica gel (approximately 50 g) and elution with ethyl acetate/hexanes [1:3] afforded the title compound (1.02 g, 70%) as a white foam: FAB LRMS (m/z, relative intensity) 530 (MH^+, 87), 529 (M^+, 100), 439 (10), 409 (10), 325 (32), 235 (20).

EXAMPLE 5

(R)-3-(N-Benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-dibenzylamino-1H-indole

To a stirred mixture of (R)-N-carbobenzyloxyproline (3.59 g, 14.41 mmol) and N,N-dimethylformamide (0.1 mL) in methylene chloride (45 mL) was added dropwise oxalyl chloride (1.87 mL, 21.62 mmol, 1.5 eq). The resulting effervescing mixture was stirred at room temperature under nitrogen for 1.5 hours. The reaction solution was then evaporated under reduced pressure, yielding the residue [(R)-N-carbobenzyloxyproline acid chloride] which was dissolved in anhydrous ether (50 mL). This solution was added dropwise to a stirred, preformed solution of 5-dibenzylaminoindole (9.00 g, 28.81 mmol, 2.0 eq) and ethyl magnesium bromide (3.0 M in ether, 10.08 mL, 30.25 mmol, 2.1 eq) in anhydrous ether (75 mL), which had been stirring at room temperature under nitrogen for 30 minutes prior to the addition of the ethereal solution of the (R)-N-carbobenzyloxyproline acid chloride. The resulting reaction mixture was stirred at room temperature under nitrogen for

30 minutes, and then ethyl acetate (100 mL) and a saturated solution of sodium hydrogen carbonate (75 mL) were added. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (100 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford a green oil. Trituration of this oil in anhydrous ether (50 mL) afforded the title compound as a white solid (3.20 g, 21%): m.p., 176.0-177.0°C; LRMS (m/z, relative intensity) 543 (100, M^+), 453 (10), 407 (7), 339 (40), 307 (10), 247 (10), 154 (38); $[\alpha]^{25}$ = +112° (tetrahydrofuran (THF), c=1.0); Anal. calcd. for $C_{35}H_{33}N_3O_3$: C, 77.32; H, 6.12; N, 7.73. Found: C, 77.35; H, 6.30; N, 7.66.

EXAMPLE 6

(R)-5-Amino-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

A mixture of (R)-5-dibenzylamino-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole (1.08 g, 2.64 mmol) and palladium [II] hydroxide on carbon (0.6 g) in absolute ethanol (25 mL) was shaken under a hydrogen atmosphere (3 atm) at 40°C for 4 hours. The resulting mixture was filtered through diatomaceous earth, and the filtrate was evaporated under reduced pressure to afford the title compound (0.60 g, 2.62 mmol, 99%) as a white foam: ^1H NMR (DMSO-d_6) δ 10.65 (br s, NH), 7.14 (d, J=2.2 Hz, 1H), 7.12 (d, J=8.6 Hz, 1H), 6.85 (d, J=1.6 Hz, 1H), 6.60 (dd, J=2.0 and 8.6 Hz, 1H), 3.63-2.83 (m, 7H), 2.78 (s, 3H), 2.05-1.67 (m, 4H); $[\alpha]^{25}$ = +9° (MeOH, c=1.0); HRMS calculated for $C_{14}H_{19}N_3$: 229.1575; found: 229.1593.

EXAMPLE 7

(R)-5-Dibenzylamino-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

To a stirred mixture of lithium aluminum hydride (0.96 g, 25.2 mmol, 2.0 eq) in anhydrous tetrahydrofuran (125 mL) at 0°C was added dropwise a solution of (R)-3-(N-benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-dibenzylamino-1H-indole (6.90 g, 12.69 mmol) in anhydrous tetrahydrofuran

(25 mL). The resulting reaction mixture was stirred at room temperature under nitrogen for 30 minutes. Lithium borohydride (0.55 g, 25.2 mmol, 2.0 eq) was then added, and the reaction mixture was heated at reflux (66°C) under nitrogen for 6 hours. The reaction mixture was cooled, and water (1.5 mL), a solution of sodium hydroxide (20%, 1.5 mL), and more water (4.5 mL) were added, sequentially. The resulting mixture was stirred at room temperature under nitrogen for 1 hour, filtered through diatomaceous earth, and the filtrate was evaporated under reduced pressure to yield a green oil (8.8 g). This oil was dissolved in absolute ethanol (90 mL), and cesium carbonate (8.0 g) and sodium carbonate (8.0 g) were added. The resulting mixture was heated at reflux for 12 hours. The reaction mixture was then evaporated under reduced pressure, and the residue was partitioned between a saturated solution of sodium hydrogen carbonate (50 mL) and ethyl acetate (100 mL). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (100 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford a brown oil. Column chromatography of this oil using silica gel (approximately 200 g) and elution with methylene chloride/methanol/ammonium hydroxide [9:1:0.1] afforded the title compound (4.63 g, 89%) as a pale green foam: ^1H NMR ($CDCl_3$) δ 7.82 (br s, NH), 7.35-7.19 (m, 10H), 7.20 (d, $\underline{J}$=8.6 Hz, 1H), 6.95 (d, $\underline{J}$=2.1 Hz, 1H), 6.85 (dd, $\underline{J}$=2.3 and 8.7 Hz, 1H), 6.80 (d, $\underline{J}$=2.2 Hz, 1H), 4.65 (s, 4H), 3.25-3.02 (m, 2H), 2.52 (dd, $\underline{J}$=9.5 and 13.9 Hz, 1H), 2.39-2.15 (m, 2H), 2.30 (s, 3H), 1.85-1.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 143.2, 139.7, 130.5, 128.5, 128.2, 127.3, 126.8, 122.9, 112.5, 112.2, 111.8, 103.4, 67.0, 57.4, 56.4, 40.6, 31.4, 29.7, 21.9; HRMS calculated for $C_{28}H_{31}N_3$ 409.2520, found 409.2475.

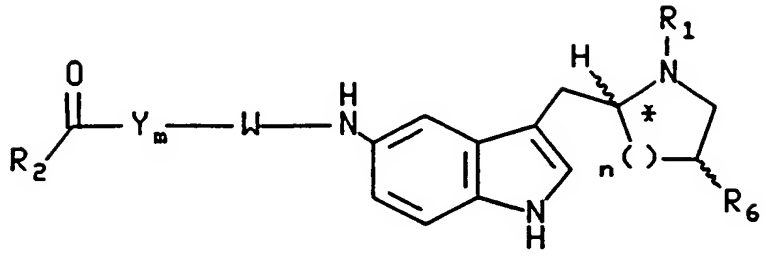
EXAMPLE 8

5-Dibenzylamino-1H-indole

To a stirred mixture of 5-aminoindole (3.00 g, 22.7 mmol) and triethylamine (10.5 mL, 74.9 mmol, 3.3 eq.) in acetonitrile (30 mL) at room temperature under nitrogen was added benzyl bromide (8.2 mL, 68.9, mmol, 3.0 eq.) dropwise. The resulting reaction mixture was heated at reflux under nitrogen for 3 hours. The resulting reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. Column chromatography of the residue using silica gel (approximately 200 g) and elution with ethyl acetate/hexanes [gradient 1:9 to 1:1] afforded the title compound as an off white solid (6.19 g, 87%): m.p., 124.0-126.0°C; ^{13}C NMR (acetone-d_6) δ 144.3, 140.8, 131.8, 129.9, 129.2, 128.3, 127.5, 125.7, 113.5, 112.4, 106.4, 101.9, 57.0; TLC [15% ethyl acetate in hexanes]: R_f=0.3.

CLAIMS

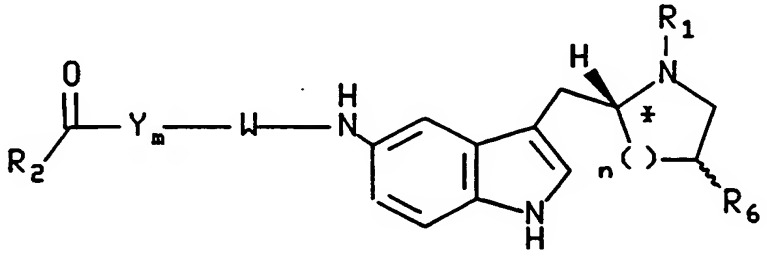
1. A compound of the formula



I

wherein n is 0, 1, or 2; m is 0 or 1; Y and W are each an amino acid residue; R_1 is hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, aryl, C_1-C_3 alkylaryl, or C_1-C_3 alkylheteroaryl, and $-(CH_2)_pR_3$; R_2 is CF_3, C_1-C_6 alkyl, aryl, C_1-C_3 alkylaryl, and $-OR_5$; R_3 is cyano, trifluoromethyl, or $-OR_4$; R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_5 is C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_6 is hydrogen, $-OR_7$, or $-NHCOR_7$; R_7 is hydrogen, C_1 to C_6 alkyl, aryl, or C_1 to C_3 alkyl-aryl; p is 1, 2, or 3; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamide, nitro, and C_1 to C_4 alkoxy and the pharmaceutically acceptable salts thereof.

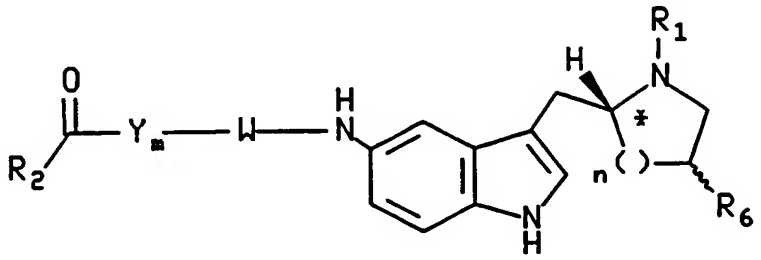
2. The compound of claim 1, wherein the compound of formula I is



3. The compound of claim 2, wherein the compound is the cis epimer.

4. The compound of claim 1, wherein the amino acid is a naturally occurring amino acid.

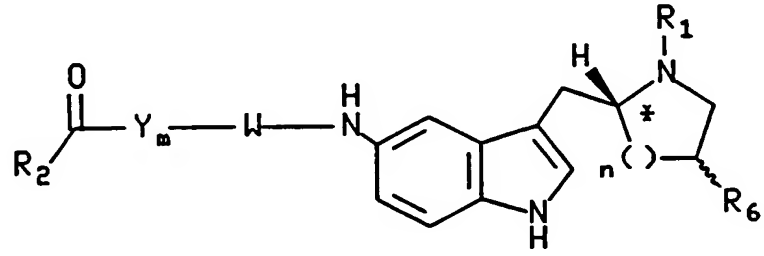
5. The compound of claim 4, wherein the compound of formula I is



6. The compound of claim 5, wherein the compound is the cis epimer.

7. The compound of claim 4, wherein the naturally occurring amino acid is alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparginine, glutamine, aspartic acid, glutamic acid, lysine, arginine, or histidine.

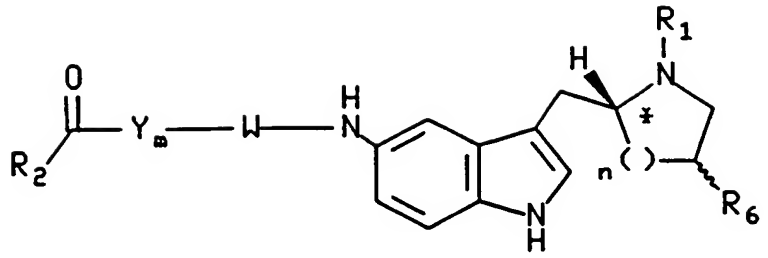
8. The compound of claim 7, wherein the compound of formula I is



9. The compound of claim 8, wherein the compound is the cis epimer.

10. The compound of claim 1 wherein n is 1; m is 0; the amino acid is a naturally occurring amino acid; R_1 is hydrogen, C_1-C_6 alkyl, or $CH_2CH_2OCH_3$; R_2 is C_1-C_4 alkyl, -Ph, $-CF_3$, or $-OR_5$.

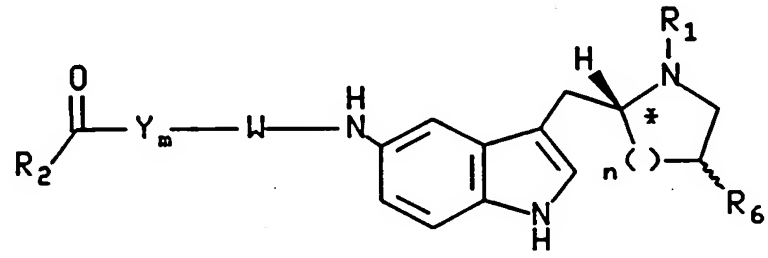
11. The compound of claim 10, wherein the compound of formula I is



12. The compound of claim 11, wherein the compound is the cis epimer.

13. The compound of claim 10, wherein the naturally occurring amino acid is alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparginine, glutamine, aspartic acid, glutamic acid, lysine, arginine, or histidine.

14. The compound of claim 13, wherein the compound of formula I is



15. The compound of claim 14, wherein the compound is the cis epimer.

16. The compound of claim 1, said compound being selected from: 5-(N-benzyloxycarbonylglycyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole; 5-(N-benzyloxycarbonyl-S-histidyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole; 5-(N-benzyloxycarbonyl-S-alanyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole; and 5-(N-benzyloxycarbonyl-S-phenylalanyl)amino-3-(N-methylpyrrolidin-2R-ylmethyl)-1H-indole.

17. A pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety,

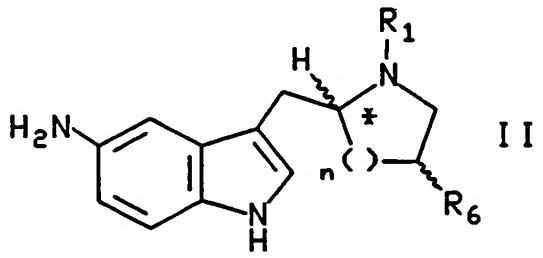
eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound according to claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission comprising an amount of a compound according to claim 1 effective in treating such a disorder and a pharmaceutically acceptable carrier.

19. A method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

20. A method for treating disorders arising from deficient serotonergic neurotransmission comprising administering to a mammal requiring such treatment as amount of a compound according to claim 1 effective in treating such condition.

21. A compound of the formula

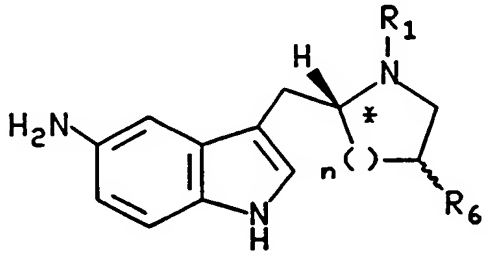


II

where n is 0, 1, or 2; R_1 is hydrogen, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, aryl, C_1-C_3 alkylaryl, or C_1-C_3 alkylheteroaryl, and $-(CH_2)_pR_3$; R_3 is cyano, trifluoromethyl, or $-OR_4$; R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_3 alkylaryl, or aryl; R_6 is hydrogen, $-OR_7$, or $-NHCOR_7$; R_7 is hydrogen, C_1 to C_6

alkyl, aryl, or C_1 to C_3 alkyl-aryl; p is 1, 2, or 3; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamide, nitro, and C_1 to C_4 alkoxy.

22. The compound of claim 21, wherein the compound of formula II is



23. The compound of claim 22, wherein the compound is the cis epimer.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D403/06; A61K31/40; C07D403/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	GB,A,2 083 463 (GLAXO GROUP LTD) 24 March 1982 see claims ---	1,17
A	GB,A,2 185 020 (GLAXO GROUP LTD) 8 July 1987 see claims ---	1,17
P,A	WO,A,9 206 973 (PFIZER INC.) 30 April 1992 * complete document * -----	1,17

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

3

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 JUNE 1993	30.06.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US93/01807

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 19 and 20 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9301807
SA 71522

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 18/06/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	7399581	18-02-82
		BE-A-	889931	11-02-82
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